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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/878,781	06/11/2001	Alexandra J. Bolton	9000-0055	1484

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 01/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/878,781	BOLTON ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77* is/are pending in the application.

4a) Of the above claim(s) *3-50,54-61,63-75 and 77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 51-53, 62 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1104,0414* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence reports (3).*

DETAILED ACTION

Preliminary Amendment

1) Acknowledgment is made of Applicants' preliminary amendment filed 09/10/02. With this, Applicants have amended the specification.

Election

2) Acknowledgment is made of Applicants' election filed 10/16/03 in response to the restriction requirement mailed 08/19/03. Applicants have elected invention I, claims 2, 52 and 53 without traverse.

Status of Claims

3) Claims 1-77 are pending.

Claims 3-50, 54-61, 63-75 and 77 are withdrawn from consideration as being directed to non-elected inventions. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claim 77 was inadvertently indicated as a linking claim to be rejoined with inventions 1-5. Since claim 77 is drawn to an antibody-containing product, it becomes a linking claim to be rejoined with one of inventions 11-15. The Office regrets this inadvertent error. Claim 77 is currently considered a non-elected.

Elected claims 2, 52 and 53, to the extent these claims encompass SEQ ID NO: 4, and the linking claims 1, 51, 62 as well as 76, the latter to the extent it encompasses SEQ ID NO: 4, are under examination. A First Action on the Merits on these claims is issued.

Sequence Listing

4) Acknowledgment is made of Applicants' submission of raw sequence listing and CRF which have been entered on 09/18/02.

Information Disclosure Statements

5) Acknowledgment is made of Applicants' Information Disclosure Statements filed 04/15/02 and 11/04/02. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Priority

6) The instant application claims domestic priority to the provisional application, 60/211,022 filed 06/12/2000.

Double Patenting Rejection(s)

7) A rejection based on double patenting of the 'same invention' type finds its support in the language on 35 U.S.C. § 101 which states that 'whoever invents or discovers any new and useful process... may obtain a patent therefor ...' (Emphasis added). Thus, the term 'same invention', in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957).

A statutory type (35 U.S.C § 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C § 101.

A) Claims 1, 2, 51-53, 62 and 76 are rejected under 35 U.S.C § 101 as claiming the same invention as that of claims 1, 2, 31, 32, 42 and 56 of the co-pending application, 10/134,297. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

B) Claim 1, 51 and 52 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of the U.S. Patent 6,660,270 ('270). Claim 76 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 3 of the U.S. Patent 6,660,270 ('270). Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims are generic to claims 2 and claim 3 respectively of the US patent 6,660,270.

Rejection(s) under 35 U.S.C § 112, First Paragraph

8) Claims 51, 52 and 62 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It is noted that the claimed vaccine comprising Streptococcus GapC protein having at least about 70% sequence identity to SEQ ID NO: 4, i.e., a GapC protein variant, and immunogenic fragments thereof comprising at least about 5 amino acids does not exist independent of its function. The specification discloses diagnostic applications or vaccine intentions for the claimed product. However, the instant specification fails to teach a single GapC protein variant having at least about

70% sequence identity to SEQ ID NO: 4, or immunogenic fragment thereof which concurrently has the ability to serve as a vaccine or a diagnostic composition. Diagnostic or vaccine applications minimally require an ability for the claimed GapC variant or fragment thereof to elicit a specific immune response, or bind specifically to an antibody. The precise structure or relevant identifying characteristics of each DNA molecule that encodes a GapC variant having at least about 70% sequence identity to SEQ ID NO: 4, or immunogenic fragment thereof, and having the immunogenic, protective or diagnostic functional activity can only be determined empirically by actually making every DNA molecule that encodes the protein variant or fragment thereof, and testing each varied DNA molecule to determine whether it encodes the recited protein variant or a fragment thereof having the particularly disclosed vaccine (protective) or diagnostic functional activity. The *Written Description Guidelines* state:

> There is an inverse correlation between the level of predictability in the art and the amount of disclosure necessary to satisfy the written description requirement. For example, if there is a well-established correlation between the structure and function in the art, one skilled in the art will be able to reasonably predict the complete structure of the claimed invention from its function.

A mere statement that the invention includes a GapC protein variant having at least about 70% sequence identity to SEQ ID NO: 4 or fragment thereof is insufficient to meet the adequate written description requirement of the claimed invention. The GapC protein variant having at least about 70% sequence identity to SEQ ID NO: 4 or fragment thereof has specific biologic properties dictated by the structure of the protein and the corresponding structure of the structural gene sequence which encodes it. A convincing structure-function relationship has to exist between the structure of the gene sequence, the structure of the protein encoded, and the function of the encoded protein. The function cannot be predicted from the modification of the structure of the gene and in the instant case, the DNA encoding the recited protein variant or fragment. Applicants have not shown that variation or modification of a reference sequence encoding a reference protein as claimed would automatically predict the production of a protein variant or fragment having the immunogenic, protective (vaccine) or diagnostic functional activity. The specification fails to teach the structure or relevant identifying characteristics of a representative number of species of DNA molecules encoding a representative number of species of protein variants, or fragments as recited, sufficient to allow one skilled in the art to determine that the inventors had possession of the invention as claimed. With the

exception of a *S. dysagalactiae* GapC protein having the amino acid sequence of SEQ ID NO: 4, a skilled artisan cannot envision the detailed chemical structure of all the protein variant or fragment species encompassed by the recited molecule. Regardless of the complexity or simplicity of the method of isolation, conception cannot be achieved until reduction to practice has occurred. Adequate written description requires more than a mere statement that its is a part of the invention and a reference to a potential method of isolating it. The nucleic acid encoding the protein variant or fragment itself is required. See *Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993)* and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.*

9) Claims 51, 52 and 62 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a GapC protein of *Streptococcus dysagalctiae* comprising the amino acid sequence of SEQ ID NO: 4, which consists of 1-336 amino acid residues, an immunogenic fragment thereof, and a vaccine composition or a kit comprising the same, does not reasonably provide enablement for a 'vaccine composition' comprising such a product, and for a vaccine composition comprising 'a Streptococcus GapC protein having at least 70% sequence identity to SEQ ID NO: 4' as claimed in claim 51(f) and an immunogenic fragment thereof as claimed in claim 51(g).

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to a vaccine composition comprising 'a Streptococcus GapC protein having at least about 70% sequence identity to (a)', i.e., a GapC protein variant, and 'immunogenic fragments of (a) .... and (f) ...said fragments comprising at least about 5 amino acids'. The protein variant and fragments as claimed, are intended for use as a

vaccine composition. A 'vaccine' by definition is required to induce a protective immune response to pathogenic *Streptococcus dysagalactiae* or a species of *Streptococcus.* The extent or degree of homology with the *Streptococcus dysagalactiae* protein having the amino acid sequence of SEQ ID NO: 4 is described to be at least 70%. Immunogenic fragments of such protein variants are claimed in claim 51(g). A polypeptide having 70% identity with SEQ ID NO: 4 will have 30% sequence dissimilarity with SEQ ID NO: 4. There is no showing that these protein variants and their immunogenic fragments retain the protective functions such that they are capable of serving as a 'vaccine'. Although a microbial polypeptide or protein is expected in the art to generally induce specific antibodies, the ability of undefined variants and 'fragments' of such a protein or polypeptide to serve as a vaccine and confer protective immunity against a microbial disease, streptococcal disease in the instant case, is not predictable. The instant specification fails to teach how to produce a Streptococcus GapC protein having 'at least about 70% sequence identity to (a)' (hereafter referred to as GapC variant), and an 'immunogenic fragment' of such a protein such that it is capable of serving as a vaccine composition and is capable of conferring immunity against streptococcal disease. The specification provides no guidance as to which specific amino acids must be retained in the GapC protein variant or 'fragment' and which may be varied or deleted without causing any detrimental effect to the claimed protein product that is meant for inducing an immune response in an animal. There is no guidance in the instant specification with regard to which amino acid variations, i.e., insertions, deletions, additions and substitutions, in the protein would result in a GapC variant or fragment protein that would retain the functional integrity or biological, antigenic and immunogenic competence of the native GapC protein, without rendering it non-functional. This is important because the art reflects unpredictability as to which amino acids in a specific protein can be varied, i.e., replaced or added, without adversely affecting the functional properties of that specific protein. While it is known in the art that variation in one or more amino acids is possible in a given protein, the exact position within its amino acid sequence where replacements or variations can be made, with a reasonable expectation of success of retaining the protein's functional competence, is not certain. A random replacement affecting the epitopic amino acid positions that are critical, for example, to the three-dimensional conformational structure and specific binding property of the protein, would result in a polypeptide that may be non-functional, or not optimally antigenic as a diagnostic reagent,

or not optimally immunogenic as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool.

Thus, the art reflects that variations in critical residues at specific positions in an amino acid sequence could result in a polypeptide which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. In the instant case, this is important because one of the purposes of the instant invention is to produce a GapC variant or fragment of the recited protein in its biologically active, immunogenic and/or protective form for inducing an immune response. The instant disclosure lacks guidance on the precise position(s), nature and extent of amino acid replacements, deletions or variations that can be made in the claimed protein or polypeptide in order to produce a GapC variant or fragment, and with regard to whether it would serve as an effective vaccine capable of conferring immunity against any streptococcal disease or *S. dysagalactiae* disease in particular, in an animal host. It is emphasized that predictability or unpredictability is one of the *Wands* factors for enablement. There appears to be no evidence that the claimed variants and fragments were indeed made and tested for their ability to serve as an effective vaccine composition by any acceptable animal model. Absent a concrete showing that the claimed variant and fragments are effective in protecting against *Streptococcus dysagalactiae* or any streptococcal infections, or eliminate or reduce morbidity and/or mortality due to such infections, the claims drawn to a vaccine are considered non-enabled. Clearly, the specification lacks adequate guidance and disclosure that would limit the experimentation from being undue. Given the art-recognized unpredictability associated with the structure-function relationship of a protein or polypeptide, one of skill in the art would look into the specification for specific teaching and guidance, which in the instant case is lacking. Due to the lack of specific disclosure as to the precise structure of the protein variant and fragments; the lack of demonstration of their antigenic, immunogenic, diagnostic and protective ability; the art-recognized unpredictability factor associated with the functions of a protein following

variation or deletion; the breadth of the claims; and the quantity of experimentation necessary, undue experimentation would have been required to practice the invention as claimed. *Ex parte Foreman*, 230 USPO 546, 547 (bd.. Pat. Appals. and Inter. 1986). The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C. § 112, first paragraph.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

10) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

11) Claims 1, 2, 51-53, 62 and 76 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant(s) regards as the invention.

(a) Claims 1, 2 and 51-53 are indefinite in the recitation "comprising ..... inclusive, of Figure 1A-1B", because it fails to point out what is included or excluded by the claim language. According to M.P.E.P 2173.05(s), where possible, claims are to be complete in themselves. Incorporation by reference to Tables, and Figures, or Examples as in this case, is a necessity doctrine, not for Applicants' convenience. See *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993). In order to obviate the rejection and since SEQ ID NO: 4 of Figure 1A-1B consists of 1-336 amino acid residues, it is recommended that Applicants replace the recitation with --comprising the amino acid sequence of SEQ ID NO: 4--.

(b) Claims 1 and 51 improperly include non-elected subject matter, for instance, parts (b)-(e) and parts of (f) or (g).

(c) Claim 76 is vague and indefinite in the recitation 'GapC protein', because it is unclear what does it represent. The origin and structure of this 'GapC protein' cannot be envisaged since it is neither identified by its structure, i.e., SEQ ID NO or by its properties, such as, molecular weight.

(d) Claims 2, 52, 53 and 62, which depend directly or indirectly from claim 1 or claim 51, are also rejected as being indefinite because of the indefiniteness or vagueness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

12) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the

basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless –
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13) Claims 1, 51, 52 and 62 are rejected under 35 U.S.C. § 102(b) as being anticipated by Boyle *et al.* (US 5,328,996 - Applicants' IDS).

Boyle *et al.* ('996) disclosed an isolated, immunogenic streptococcal protein comprising an amino acid sequence identified as SEQ ID NO: 2 that is 99.8% identical to the instantly recited SEQ ID NO: 4 for use as a vaccine. A vaccine composition comprising the same in PBS or an adjuvant is taught (see claim 1; column 2, lines 37-42 and 55 and 56; Materials and Methods; and Examples 14 and 21; and the attached Sequence search report).

Claims 1, 51, 52 and 62 are anticipated by Boyle *et al.* ('996).

14) Claims 1, 51, 52, 62 and 76 are rejected under 35 U.S.C. § 102(b) as being anticipated by Choi *et al.* (WO 98/18930 - Applicants' IDS).

It is noted that the generic protein of unspecified origin recited in claim 76 is neither structurally identified by a SEQ ID number, nor by any structural property, such as, molecular weight.

Choi *et al.* disclosed isolated streptococcal antigenic peptides or epitope-containing fragments and a vaccine comprising the same with or without an adjuvant. A sequence search performed in the Office shows that one of the prior art peptides has 100% sequence or structural identity with a fragment of the instantly recited SEQ ID NO: 4 (see pages 21-28 and 36-41; claims 1, 2, 16 and 20; and the attached sequence search report). The prior art peptide or epitope-containing fragment comprises at least five amino acid residues of SEQ ID NO: 4. A kit comprising the whole protein or a peptide thereof for use in immunodiagnosis of a streptococcal infection is taught (see page 35 and claim 20).

Claims 1, 51, 52, 62 and 76 are anticipated by Choi *et al.*

Remarks

15) Claims 1, 2, 51-53, 62 and 76 stand rejected.

16) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The

transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The TC 1600 facsimile center receives transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

17) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347 until Janaury 2004 and (571) 272-0854 beginning February 2004. The Examiner can normally be reached on Monday to Friday from 7.45 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER